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Anemia, Genetic Diseases, and Malaria in Prehistoric Mainland Southeast Asia

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KEY WORDS Thalassemia, Abnormal hemoglobins, Environmental adaptation, Thailand

ABSTRACT The analysis of a sample of skeletons from the 4,000-year-old site of Khok Phanom Di on the coast of central Thailand has identified a number of individuals with skeletal evidence suggestive of severe anemia. The differential diagnosis of the lesions is discussed and the presence of one of the thalassemia syndromes is proposed. The implications of this for southeast Asian prehistory are discussed. The presence of these conditions has been suggested in previous analyses of prehistoric southeast Asian populations, but this is the first population in which the evidence, including post-cranial responses, is presented in detail.

Skeletal pathology believed to be indicative of marrow hypertrophy stimulated by chronic, severe anemia has been described in prehistoric populations from many areas of the world, including the Mediterranean (Angel, 1984; Hershkovitz et al., 1991), South America (Hrdlicka, 1914), North America (El-Najjar et al., 1975), Australia (Webb, 1990), and southeast Asia (Sangvichien et al., 1969). In a sample of skeletons from the 4,000-year-old site of Khok Phanom Di in central Thailand (Higham and Bannanurag, 1990), a number of individuals have bony pathology suggestive of anemia. The pathology is described in this paper, the differential diagnosis is discussed, and the wider implications for the community are also considered.

THE SITE AND THE PEOPLE OF KHOK PHANOM DI

Khok Phanom Di is approximately 100 km southeast of Bangkok and 20 km from the coast of the Gulf of Thailand. The site is a 12 m high mound, aproximately 5 ha in area, composed largely of culturally deposited material. In 1985, a 10 × 10 m square on the top of the mound was excavated to the base of cultural deposits at a depth of 7 m. The stratigraphy was clear and largely undisturbed. One hundred and fifty-four burials were found in an almost continuous sequence through 6 m of deposits. Although the exact time depth represented is not known, radiocarbon dates suggest it is about 500 years, from 2000 to 1500 BC (Higham and Bannanurag, 1990).

Paleoenvironmental evidence suggests that during the initial period of occupation Khok Phanom Di was on or near a river channel (Mason, 1991; Thompson, 1996) and closer to the coast than at present, with the river channel forming part of the drainage system of what is now the Bang Pakong Valley. The first occupants of the site were living in an area where the original forest vegetation had been modified to encourage the growth of open land species (Maloney, 1991). The local environment included brackish and freshwater swamps, mangroves, and dry salt flats. Coastal, estuarine, and riverine

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resources were accessible from the site (Mason, 1991; Thompson, 1996). Over time, there appears to have been a change in the environment involving coastal progradation and a probable change in the drainage pattern. The resource spectrum changed, with a reduction in access to marine resources associated with increased access to freshwater environments (Mason, 1991; Thompson, 1996). Food debris indicates that the diet included fish, crustaceans, and molluscs, and a relatively limited amount of meat from terrestrial animals. The vegetable component of the diet included domesticated rice (Thompson, 1996) and probably a variety of other vegetable foods which grow in the vicinity of the site at present. This diet would have been nutritionally adequate in both protein and calories, although the monsoon climate would have meant that the supply of some foods was seasonal. Despite this, aquatic foods and some of the plants would have been available year round.

Most burials at the site were undisturbed and, as conditions were ideal for bone preservation, most of the skeletons were complete and in very good condition. Similar features of the mortuary practices were present in all levels of the cemetery and this, together with continuity in the cultural deposits, suggests occupation of the site by generations of a single, sedentary group. The sample includes a high proportion of infants (48% died before the age of 5 years), but few individuals between the ages of 5 and 25 years. The mean estimated age at death of adults (>15 years) is 30.5 years, with the oldest individual 50+ years. Although it is high, the proportion of infants is within the range which could be expected in such a population (Weiss, 1973). Males and females were represented almost equally in the adults. The overall age and sex composition of the sample indicates that it is likely to be representative of the cemetery population. Methods of age and sex estimation and details of sample composition are available in Tayles (in preparation).

The recording and interpretation of skeletal pathology at Khok Phanom Di was not approached as a discrete exercise but was contained within a holistic study of the health of the people, taking into account characteristics such as age at death, stature, bone mass, and evidence of growth disruption as indicated by lines of arrested growth and enamel hypoplasia. All bones were examined in detail for pathology. Pathology reflecting trauma, or age- or activity-related degeneration of the musculoskeletal system, is excluded from the following discussion.

SKELETAL PATHOLOGY

In some infants and children, the subperiosteal bone of the upper orbits has the thickening, porosity, and cribrotic bone formation typical of "cribra orbitalia" (Stuart-Macadam, 1985). Of 13 children aged between 1 and 14 years with the orbital roof intact, 10 had orbital changes (77%), including seven of the eight children aged over 5 years. Using the scale of severity listed by Stuart-Macadam (1985), two had light, three had medium, and four had severe cribra orbitalia. None of the children less than 1 year old (n = 63) was affected. Of the adults, three (of 57 with the orbital roof intact = 5%) had light cribra orbitalia. These individuals, two males and one female, all died by their mid-20s. The thickness of the orbital roof was measured on cephalographs of the Khok Phanom Di children using the methods of Stuart-Macadam (1987a), and correcting for radiographic enlargement. None reached more than 1 mm thickness. Although no standards for the thickness of this structure in children in general has been found, our measurement is well below the 3 mm thickness found by Stuart-Macadam (1987a) to be more prevalent in children with cribra orbitalia than in children without the evidence of anemia.

Three infants (Burials 101, 121, 150; aged 15–30 months) have craniofacial bones which are thicker than those in other infants in the sample and in crania of normal infants in the collection in the Anatomy Museum at the University of Otago. The anterolateral sections of the frontal bones and the zygomatic bones have hypertrophied. This is particularly evident in the anteroposterior dimension of the zygomatic bones, with rounded edges on the orbital rim and inferior margins (Figs. 1, 2). These infants also have thin cortices and enlarged medullary cavit-

ies on long bones compared with long bones from other infants in the Khok Phanom Di sample (Fig. 3).

In an infant aged about 1 year (Burial 88), the cortices of the long bones are extremely porous, with extensive proliferation of subperiosteal reactive bone on the shafts of the limb bones and the clavicles. The bones involved are illustrated on Figure 4. The proliferation extends in a radial arrangement, and is distinct from the cortical bone (Fig. 5). There is no evidence of diploic expansion on the fragments of cranial vault which are present, or of cribra orbitalia or hypertrophy of the bones of the facial skeleton. The medullary cavities of the long bones are not unusually large (Fig. 6).

An 8-year-old child (Burial 21) has several of the middle and distal hand phalanges and the fifth metatarsals with hypertrophied shafts and gross porosity of the cortical bone (Fig. 7). Nutrient foramina in the shafts of the fifth and fourth metatarsals and in some hand phalanges are enlarged. There is a lesion on the nasal bones, with enlargement of the vascular foramina, porosity, and irregular formation of bone on the subperiosteal surface. This child had severe cribra orbitalia.

In the postcranial skeleton, four of the eight children aged over 5 years had enlarged nutrient foramina on the hand phalanges (Fig. 8).

A young adult male (Burial 24) has one humerus 17 mm shorter than the other, with the head slightly angled medioinferiorly (Fig. 9).

The thickness and structure of the cranial vault was investigated on parietal fragments from broken crania of adults. The total thickness of the vault was measured and the ratio of diploe to cortical bone calculated. In nine of 10 females in the sample the vault thicknessess ranged from 6.5 mm to 9.7 mm, with a mean of 8.4 mm (SD 1.6), and in all males ($n = 5$) the range was 6.3–9.5 mm, with a mean of 7.5 mm (SD 1.3). The ratio of diploe to cortical bone was less than 2.5:1 in all except one female. The exceptional individual was an older female (Burial 56) with a parietal thickness of 11.7 mm and a ratio of diploe:cortical bone of 3.6:1 (Fig. 10).

Vault thickness was also measured on lateral cephalographs of intact crania, although the bone was too dense for the internal structure of the vault to be visible. Measurements were taken at the midfrontal point, at bregma, and at vertex. Maximum thicknesses were 11–12 mm at bregma and vertex (Table 1).

The internal structure of the vault was visible on cephalographs of four children with intact crania. The ratio of diploe to cortical bone (inner and outer tables combined) at midfrontal ranged from 0.68:1.00 to 1.21:1.00.

The evidence from the individuals described above is summarized in Table 2.

INTERPRETATION/DIFFERENTIAL DIAGNOSIS

Of the lesions described in the previous section, cribra orbitalia is the most prevalent. The basis of development of this skeletal reaction and its association with anemia has recently been comprehensively demonstrated by Stuart-Macadam (1987b). The children from Khok Phanom Di with the cribra orbitalia may therefore be diagnosed as having suffered from anemia, although the condition is not specific to any one type of anemia but rather a generic skeletal reaction.

Facial changes specific to some of the genetic anemias such as thalassemia are identified in early clinical reports (Baker, 1964; Caffey, 1951; Weatherall and Clegg, 1981). These changes reflect hypertrophy of the marrow in the facial bones and result in a facial morphology variously described as "mongoloid" or "rodent facies." As the maxillae enlarge, the midface broadens, the eyes become widely spaced with a "mongoloid" slant, and the bridge of the nose is flattened. These effects reduce the age (Baker, 1964; Caffey, 1951). No other diseases are known to produce the same response. The hypertrophy described in the facial bones of infants from Khok Phanom Di is believed to be evidence of this skeletal response to marrow hypertrophy reflecting anemia.

In the vault of Burial 56, the ratio of diploe to cortical bone is considerably greater than the maximum ratio of 2.3:1 in a series of normal individuals reported by Reynolds

Figure 1

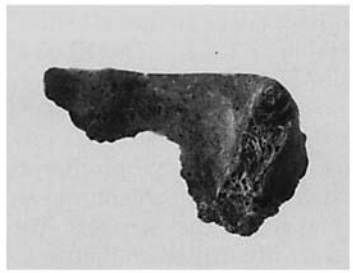

Figure 2

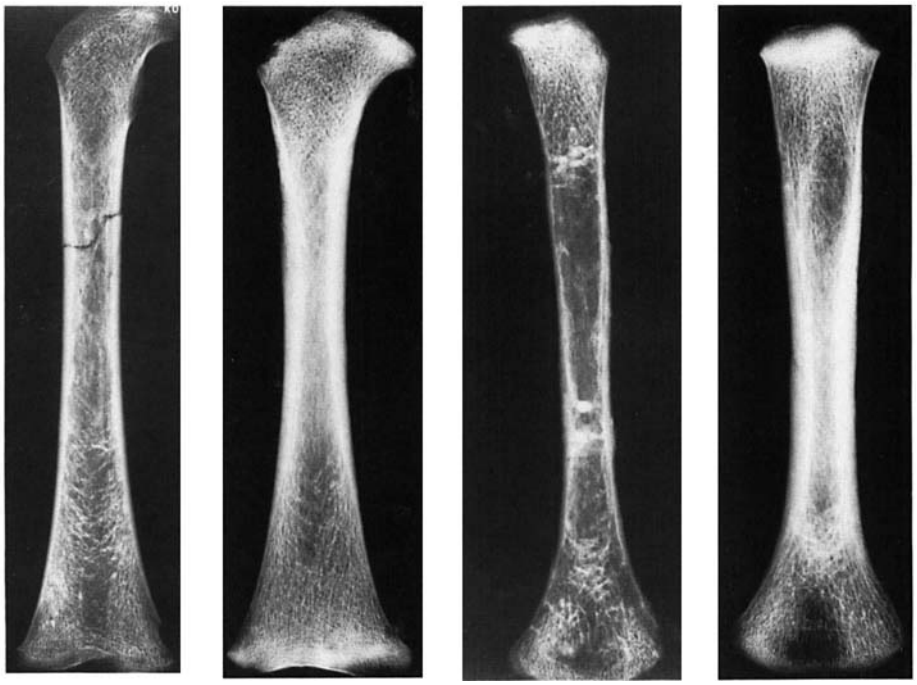

Figure 3

(1965). Diploic expansion is a feature of the marrow hypertrophy in anemic individuals.

The enlarged nutrient foramina in the small bones of the hands and/or feet of several children suggests increased vascularity. This response has been recorded in cases of genetic anemias such as thalassemia, sickle-cell anemia and variants, and in hemophilia, Gaucher disease, and leprosy (Fink et al., 1984; Lawson et al., 1984).

The extreme cortical porosity and subperiosteal bone formation (periostitis) in the limb bones of Burial 88 are nonspecific conditions which may have several alternative diagnoses. These include infantile cortical hyperostosis, hypervitaminosis A, yaws, osteomyelitis, and genetic anemia. Infantile cortical hyperostosis, a poorly understood condition of "obscure pathogenesis" (Silverman, 1985:841), produces subperiosteal new bone formation on the diaphyses of long bones (especially the tibia), the mandible, clavicle, and occasionally the scapula and ribs. The distribution of the subperiosteal new bone can be variable (Jaffe, 1972; Silverman, 1985). The cortical new bone can become profuse, increasing the cortices to more than twice the original thickness. The metaphyses or epiphyses are not affected. The disease develops early in infancy, rarely later than 5 months of age, and usually resolves within some months of diagnosis. It has not been recognized as a direct cause of fatality. A familial form of the condition has been recognized (McKusick 1992; MacLachlan et al., 1984). There is "probably" also a sporadic form of unknown pathogenesis (MacLachlan et al., 1984). The condition was only recognized and recorded in the 1930s and 1940s. Since then the number of cases recognized as hereditary has increased and recently no "sporadic" cases have been recorded (MacLachlan et al., 1984). The presence of the cortical hyperplasia in only one infant at Khok Phanom Di suggests that the familial form of the disease can be discounted. There is very little written about the sporadic form and despite an extensive search of the literature no estimate of its incidence or details of environmental factors triggering the condition have been found, other than a single case of prenatal iatrogenic origin (Pazzaglia et al., 1985).

Hypervitaminosis A can also induce the development of subperiosteal new bone, with the ulnae and metatarsals typically involved. The clavicles, tibiae, and fibulae are also commonly affected, the femora, humerii, metacarpals, and ribs less commonly, and the mandible rarely. The metaphyses and epiphyses are not usually involved (Resnick and Niwayama, 1981). Reported clinical cases involve overdoses fed to children by misguided parents. The liver of certain species of fish is high in vitamin A and occasionally hypervitaminosis is developed by eating fish liver (Higashi, 1961). It has also been recorded in infants fed chicken livers (Silverman, 1985). An unusual diet is clearly required to produce this condition.

Yaws, a treponemal infection found in southeast Asia today, can also produce bony changes in its early stages which include diaphyseal periostitis, particularly in young children (Hackett, 1976). Osteomyelitis can also produce periostitis (Jaffe, 1972; Ortner and Putschar, 1981; Silverman, 1985). However, gross porosity is not a characteristic of this infection and there is no evidence on the skeleton of Burial 88 of the cloacae, sequestra, or involucra which are other bony responses. The widespread distribution of lesions on the child is hardly compatible with survival in osteomyelitis.

Subperiosteal new bone formation on the shafts of long bones, similar in appearance to the "hair-on-end" arrangement of cranial subperiosteal bone in some cases of thalassemia, has been described in Thai children

Fig. 1. Anterosuperior view of infant zygomatic bones. The two upper bones (Burials 101, 121) show hypertrophy and rounded contours compared with the more angular outline of the two normal bones from infants of the same age from Khok Phanom Di (lower).

Fig. 2. Inferior aspect of anterolateral frontal bone of infant Burial 121 (upper) and normal infant of the same age (lower). The bone from Burial 121 illustrates hypertrophy at the zygomatico-frontal suture compared with the normal bone. Porosity indicating cribra orbitalia is also visible in the orbital roof.

Fig. 3. Anteroposterior radiograph of infant humeri and femora from Khok Phanom Di. The bones on the left in each case (femur Burial 150; humerus Burial 121) illustrate thinned cortices and widened medullary cavities compared with the normal bones on the right from infants of the same age.

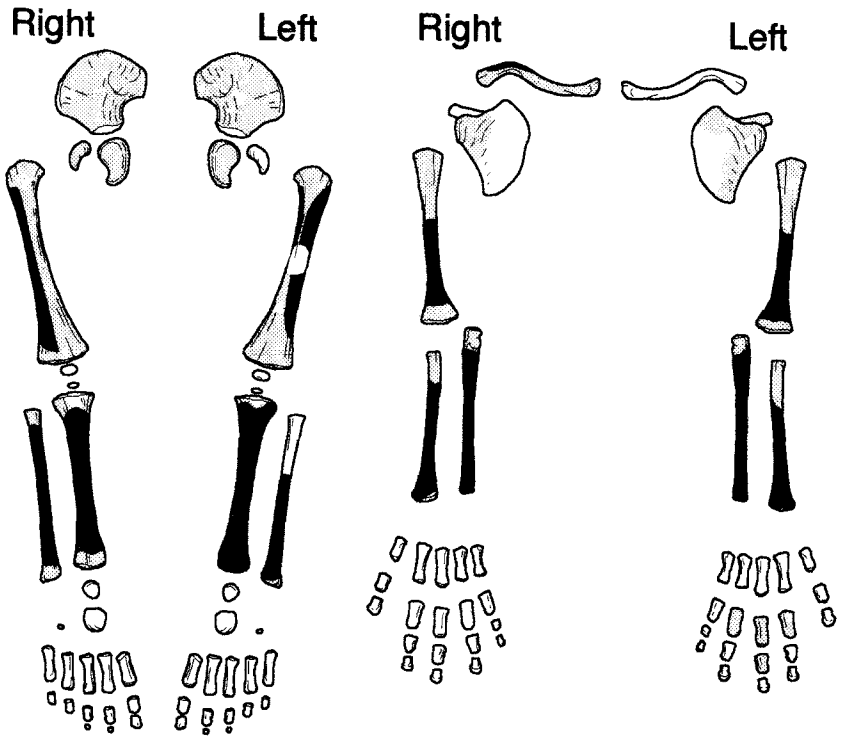

Figure 4

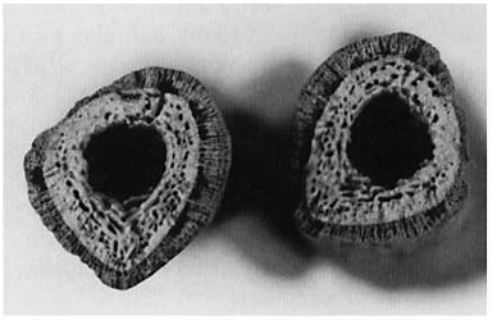

Figure 5

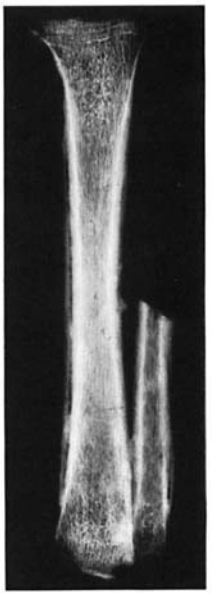

Figure 6

with hereditary anemia (Singcharoen, 1989).

In the case of Burial 21, the child with hand and foot changes, conditions which need to be considered in differential diagnosis again include treponemal infection, osteomyelitis, and chronic, severe anemia. Early infections of the treponemal infection, yaws, can produce dactylitis (Hackett, 1957). The pattern may be not unlike that seen in Burial 21. Osteomyelitis is unlikely to be responsible in this case as such gross cortical porosity in the absence of sequestra and cloacae is not a characteristic of this infection (Silverman, 1985). The extreme porosity of the cortex of some of the small bones of the hands and feet and the enlarged nutrient foramina are consistent with aspects of the bony responses described in classical clinical reports of children with chronic or severe anemia (Caffey, 1951, 1957), although the medullary cavity is not greatly enlarged. The changes closely resemble the illustration of the hand of a 14-year-old child with thalassemia who had been on a low transfusion regime (Scutellari et al., 1989). That is, the degree of erythroid hyperplasia and the stage of regression of the red marrow from the appendicular skeleton is relevant in determining the bony changes which may be initiated.

In the case of Burial 24, the adult with a misshapen humerus, differential diagnoses include trauma, infection, and anemia. Fracture of the epiphyseal cartilage plate of the proximal humerus can occur during the growth period (Dameron and Reibel, 1969). The long-term skeletal response in untreated cases is not known, but with nonsurgical treatment involving immobilization the damage can result in shortening of the bone. The age at which the injury is sustained influences the results, but older children can suffer permanent angular deformity (Dameron and Reibel, 1969). Infection can also result in permanent deformity, as osteomyelitis during infancy can spread to the cartilaginous growth plate with subsequent disturbances of growth (Resnick and Niwayama, 1981). Both fracture and infection result in reactive bone growth. There is no evidence on Burial 24 of reactive bone on the proximal humerus, although this does not exclude the possibility that trauma or infection occurred during early childhood, with subsequent complete remodeling.

Premature fusion of the proximal epiphysis of the bone is relatively common in individuals suffering from thalassemia (Currarino and Erlandson, 1964; Exarchou et al., 1984). Clinicians have reported up to 26% of patients with homozygous beta-thalassemia (n = 16/62) (Exarchou et al., 1984) having deformities of the humerus resulting from premature fusion of the epiphysis. The severity of the anemia is apparently not a factor in the development of this condition (Exarchou et al., 1984). A case from the prehistoric Middle East similar to Burial 24 has been described by Hershkovitz et al. (1991).

When making a diagnosis from conditions which are not pathognomonic, as in the cases of Burials 88, 21, and 24, other factors such as frequency and distribution of the disease in the population need to be taken into consideration.

In the diagnosis of the cortical hyperostosis of Burial 88, the absence of other examples in the population is relevant. It is unlikely that a single case of either the familial form of infantile cortical hyperostosis or hypervitaminosis A would exist in a population this size. The sporadic form of infantile cortical hyperostosis cannot be entirely discounted. Yaws is a possible explanation for the lesions in both Burial 21 and Burial 88. It is a disease easily transmitted within the home and its surroundings, and common among those engaged in agricultural work such as rice growing (Bruce-Chwatt, 1978). In living populations, before the advent of antibiotics, seropositivity in adults in endemic areas was as high as 80% (Hackett, 1947). Clinical estimates of the prevalence of bony changes in individuals with yaws suggest about 1–5% will be affected (Ortner

Fig. 4. Upper and lower limbs of Burial 88, showing the skeletal elements present (light shading) and distribution of reactive periosteal bone (dark shading).

Fig. 5. Cross-section of tibia of Burial 88, showing grossly porotic cortex and proliferation of reactive radial subperiosteal bone.

Fig. 6. Anteroposterior radiograph of Burial 88 tibia and part of fibula, showing the deposition of reactive subperiosteal bone.

Figure 7

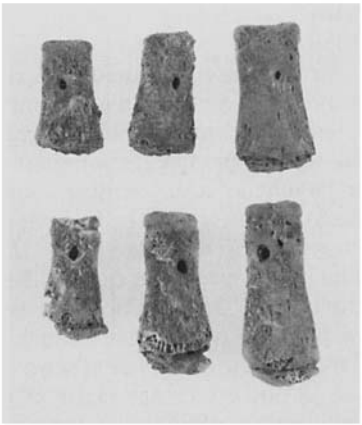

Figure 8

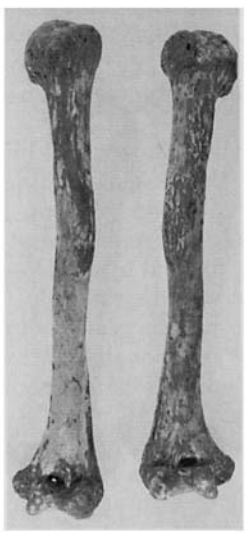

Figure 9

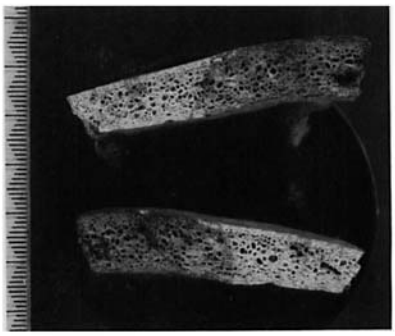

Figure 10

TABLE 1. Adult cranial vault thickness measurements from lateral cephalographs (mm)[1]

	Midfrontal	Bregma	Vertex
Females (n = 18)			
Mean	7.7	6.9	7.5
Standard deviation	1.7	1.5	1.3
Minimum	5.6	5.4	5.7
Maximum	12.3	11.2	10.2
Males (n = 11)			
Mean	7.5	8.7	9.0
Standard deviation	1.1	1.9	1.3
Minimum	5.4	5.6	7.3
Maximum	8.6	12.1	11.4

[1] Measurements in millimeters, from lateral cephalographs, adjusted for radiographic enlargement. Vertex = the highest point of the calvarium, measured perpendicular to a line drawn between porion and orbitale. Midfrontal = midway between bregma and nasion.

and Putschar, 1981; Rothschild and Heathcote, 1993). The rate can be expected to be higher in skeletal populations, where lesions are identifiable at an earlier stage than from radiographs of living individuals. Reports indicate that the rate in skeletal populations ranges from 20% in individuals over the age of 10 years (Rothschild and Heathcote, 1993) to 80% (Houghton, 1996). The complete absence of any relevant bone changes, either active or inactive, in the population from Khok Phanom Di aged 10 years or more (n = 74) argues against treponemal infection as an explanation in Burials 21 and 88.

The prevalence of cribra orbitalia suggests that anemia was suffered by a proportion of the subadult population. The discussion of the other skeletal pathologies offers several alternative diagnoses in each case, but a consistent factor is that anemia is one of the alternatives. Accounting for all the lesions without considering anemia would require the suggestion that a variety of infections were present in the population and leave some cases undiagnosed.

Fig. 7. Metatarsals from Burial 21. The fifth metatarsals have hypertrophied shafts and grossly porotic cortices.

Fig. 8. Hand phalanges from children illustrating enlarged nutrient foramina (lower) compared with normal foramina (upper).

Fig. 9. Humeri from Burial 24. One bone is shorter than the other and the head is angled antero-medially.

Fig. 10. Cross-section of vault of Burial 56 showing hypertrophy of the diploe and thinning and porosity of the outer table. The discoloration on the bone is postmortem.

In some of the individual cases discussed, there are other factors which are consistent with the diagnoses of anemia. Burial 21 has cribra orbitalia, which is consistent with the anemia hypothesis. Burial 24, in addition to the pathology in the humerus, was the shortest male in the Khok Phanom Di sample (estimated stature 1,538 mm; population male mean 1,622 mm; SD 51 mm). This short stature is consistent with the growth retardation commonly associated with thalassemia. Burial 56, with expanded diploe, was by far the smallest of the females (1,411 mm; population mean 1,543 mm; SD 45 mm), a factor which may also reflect growth retardation.

DISCUSSION

Skeletal response to anemia is secondary to hypertrophy of hemopoietic bone marrow as activity increases to compensate for the ineffective erythropoiesis or hemolysis (premature destruction of erythrocytes) causing the anemia (Dacie, 1985; Moseley, 1974; Weatherall and Clegg, 1981). In a majority of reports on prehistoric skeletal remains, the identification of skeletal response to anemia has been based on cranial evidence. Comparatively few reports consider postcranial evidence for anemia. There are several factors which may have contributed to the concentration on cranial evidence. In children, hemopoietic (red) marrow is distributed throughout the skeleton. Accordingly, any part of the skeleton, and the limbs in particular, may be affected by the hypertrophy of the marrow. By adulthood, red marrow has been replaced by fatty yellow marrow in all but the axial skeleton (Williams et al., 1989). The cranium is the most likely site of remaining grossly visible bony evidence. The preferential survival of adult skeletons and collection of crania in particular probably contributed to the anthropological concentration on the analysis of crania prevailing in the late 19th and early 20th century when porotic hyperostosis (under a variety of names) and cribra orbitalia were first recognized and described [e.g., Hrdlicka, 1914; Welcker, 1888 (cited in Stuart-Macadam, 1989)].

Bony evidence in the cranium is most com-

TABLE 2. Individuals with skeletal pathology suggestive of anemia

Burial no.	Sex, age	Evidence of anemia	Evidence of general health
21	Child, c. 8 years	Moderate cribra orbitalia; extreme cortical porosity and thinning, hand phalanges, and fifth metatarsals	
24	Male, c. 25 years	Malformation of proximal humerus	Short stature
56	Female, c. 45 years	Cranial vault with expanded diploe and thin tables	Very short stature, thin cortices on long bones
88	Infant, 9 months	Porotic cortical bone, radial periosteal bone proliferation on long bones	Dental enamel hypoplasia
101	Infant, 15 months	Hypertrophy of craniofacial bones (especially anterior frontal bone)	
105	Infant, 3 months	Hypertrophy of craniofacial bones (especially anterior frontal bone)	
121	Infant, 15 months	Hypertrophy of craniofacial bones including maxilla, zygomatic, temporal, greater wing of sphenoid, frontal (anterolateral); moderate cribra orbitalia	Dental enamel hypoplasia, osteoporosis
150	Infant, 30 months	Hypertrophy of craniofacial bones: frontal, zygomatic	Osteoporosis

mon in the anterior cranial fossa, where the orbital plate of the frontal bone forms the roof of the orbits. The orbital plate may hypertrophy to accommodate the expansion of the marrow within its normally closely apposed tables. The effect on the structure is that the subperiosteal surface of the inferior table becomes firstly porous and secondly develops radiating bone growth, producing "cribra orbitalia." A similar response is produced in the cranial vault in the form of grossly visible external porosity, thinning of the external table, expansion of the diploe, and thickening of the trabeculae with reduction in the number and radial arrangement of those remaining (Ortner and Putschar, 1981; Stuart-Macadam, 1987a, 1992). These bone changes together produce the grossly visible condition most commonly described "porotic hyperostosis" in the anthropological literature (Angel, 1966; Stuart-Macadam, 1985, 1987a,b, 1989, 1992).

These cranial reactions are both external and conspicuous compared with many of the less distinctive postcranial changes which are mainly visible only radiographically. In addition to cranial evidence of anemia, Angel (1966, 1971) has described postcranial evidence in infants and children from prehistoric sites in the Mediterranean, in the form of an "inner shell" of unremodeled lamellar bone within the shafts of some long bones, although it is not clear why this should occur. The infants and children are believed to have been suffering from hereditary anemia.

Clinical reports show that there can be considerable variation among individuals in the degree and nature of the skeletal response to anemia, and that this is not necessarily reflective of the degree and nature of the anemia. Descriptions of cranial reaction are based mainly on radiographs and concentrate on the changes in the diploe and cortex described above. Mild to extreme involvement of the cranium has been recorded in both genetic anemia and iron-deficiency anemia (Lanzkowsky, 1968; Lie-Injo, 1958; Moseley, 1971; Weatherall and Clegg, 1981). The early stages of these vault changes are given less emphasis in clinical reports than in skeletal reports. Many texts describe the appearance of "hair-on-end" seen on radiographs in extreme cases where the outer table has been resorbed and the diploe expanded with trabeculae radially oriented. However, this condition is not typical, as it is present in only 5–20% of clinical cases (Fernbach, 1984; Scutellari et al., 1989; Silverman, 1985). Generalized osteoporosis is much more common, although definitely less spectacular and much more difficult to differentiate from the normal appearance of the cranial vault on radiographs. Other cranial changes reported include enlarged vascular impressions on the internal table (Lawson et al., 1984) and "onion-skin"

layering of the vault (Orzincolo et al., 1989). Internally, pneumatization of the paranasal sinuses and development of the mastoid air cells may also be retarded (Caffey, 1951; Fernbach, 1984; Weatherall and Clegg, 1981).

Postcranial changes generally reflect the same marrow hyperplasia, with expansion of the medullary cavity in long bones accompanied by reduction in distribution and coarsening of trabeculae, and extreme thinning and porosity of cortices (Baker, 1964; Caffey, 1951; Weatherall and Clegg, 1981). The marrow hypertrophy is accompanied by increased vascularity, resulting in the enlarged nutrient foramina in the phalanges (Fink et al., 1984; Lawson et al., 1984; Middlemiss and Raper, 1966). Overall skeletal growth and maturation can also be retarded in severely anemic individuals (Laor et al., 1982; Weatherall and Clegg, 1981).

Age at death is relevant to the nature of bony change which may be expected in an individual. The regression of hemopoietic marrow from the appendicular skeleton during childhood is one factor. Individuals who are not severely affected by anemia and so have survived childhood could be expected to show a different set of skeletal changes, if any, from those evident in children. The greater prevalence of skeletal changes suggestive of anemia in the Khok Phanom Di children than in adults is consistent with the skeletal response to the disease. In adults, any bony changes occurring during childhood are likely to have been remodeled to a large extent, if not completely.

Many of the clinical reports of cases in older children and young adults, particularly in recent years, are of individuals with severe anemia who have been treated with blood transfusions. Cases of mild anemia are not of the same clinical interest. The bony changes in the reported cases are not necessarily directly comparable with prehistoric evidence from individuals of a similar age. Without treatment, many children and infants with a severe manifestation of the disease would have died at an earlier age.

Conversely, it also needs to be considered whether the cause of death in children in these circumstances is not necessarily the anemia but any one of the infections, such as intestinal parasites, to which children in tropical climates could have been exposed. Anemic children are particularly susceptible to infection (Weatherall and Clegg, 1981), and therefore the extent of bony changes consequent on the anemia are not necessarily correlated with age at death.

Skeletal changes occur only in certain anemias. Although there are various causes of anemia, skeletal changes have been clinically reported only in individuals with inherited disorders of hemoglobin and acquired chronic iron deficiency anemia (Stuart-Macadam, 1992). There are some secondary skeletal reactions such as bone infarctions which are specific to particular genetic anemias (Moseley, 1974). Except where these secondary reactions have occurred, identification of the etiology of the anemia is difficult on the basis of skeletal pathology alone.

On the basis of skeletal evidence, the etiology of at least some of the cases of anemia at Khok Phanom Di appears to have been genetic anemia. This includes the infants with hypertrophy of the facial bones. Hypertrophied facial bones ". . . almost certainly establish the diagnosis of thalassemia major" (Moseley, 1971:698). The Khok Phanom Di infants with hypertrophy of the facial bones have no evidence of cribra orbitalia or porotic hyperostosis of the vault. Again, the age at death may be the relevant factor in the nature of the skeletal response. Hypertrophy of the facial bones was not evident in older children at Khok Phanom Di, although several, including those with cribra orbitalia, had wide, flat faces with prognathic maxillae. The "mongoloid" features of thalassemics are clearly evident in Caucasian children, but are characteristic of the normal facial morphology of Asians so it is difficult to identify the limits of normal variation. This factor has also been noted in clinical reports of modern Thai children (Chernoff et al., 1956). In the absence of readily accessible detailed data on the range of normal dimensions of the juvenile southeast Asian face, these features could not be accepted as conclusive evidence that this morphology represented a departure from the normal.

Similarly, as no data on the "normal" range of variation of thickness of the cranial vault or of the diploe to cortical bone in children has been found in the literature, measure-

TABLE 3. Thickness of the cranial vault (mm); measurements from cephalographs (corrected for radiographic enlargement) or direct from crania in some skeletal samples[1]

			Midfrontal		Bregma		Vertex	
Females	Years B.P.	n	Mean	SD	Mean	SD	Mean	SD
Khok Phanom Di[2]	4000–3500	18	7.68	1.65	6.91	1.47	7.47	1.30
Australian Aborigine[3]	Pleistocene	8	8.40	1.73	8.40	1.07	7.40	0.50
	Recent	52	7.50	1.35	7.80	1.39	7.70	1.35
Japanese-Jomon[4]	6000–2000	18	—	—	7.90	1.87	—	—
	Modern	47	—	—	6.00	1.20	—	—
Near East[5]	1550–2200	5	—	—	5.10	1.00	4.90	1.30
	Recent	12	—	—	6.10	1.10	5.10	1.00
Males								
Khok Phanom Di[2]	4000–3500	11	7.45	1.09	8.67	1.88	9.00	1.29
Australian Aborigine[3]	Pleistocene	20	10.40	2.41	10.80	1.93	9.20	1.68
	"	4	8.70	1.64	10.10	1.44	9.70	3.04
	Recent	47	7.80	1.58	8.90	1.50	8.70	1.44
Japanese-Jomon[4]	6–2000	26	—	—	8.80	1.34	—	—
	Modern	105	—	—	6.30	1.26	—	—
Near East[5]	1550–2200	11	—	—	6.40	1.90	6.80	1.60
	Recent	11	—	—	5.60	1.80	5.40	1.20

[1] Sites of measurement as for Table 2.
[2] Tayles, in press.
[3] Brown, 1987.
[4] Ishida and Dodo, 1990.
[5] Smith et al., 1985.

ments of vault thickness or ratios are not diagnostic. On the basis of qualitative assessment, none of the children with cribra orbitalia had porotic hyperostosis of the cranial vault. Stuart-Macadam (1992) notes the possibility that the two areas of the skull can respond independently, and that lesions in the orbit commonly occur without the vault being affected.

The maximum thickness of the cranial vaults of adults at Khok Phanom Di is within the ranges of various prehistoric populations in Australia (Brown, 1987), Japan (Ishida and Dodo, 1990), and the Near East (Smith et al., 1985) (Table 3). There is no reason to believe that the thicknesses of the vaults of the Khok Phanom Di crania are beyond the range of normal in prehistoric populations, despite the variation which is present. The normal clinical pattern for diploic expansion in anemic individuals is for the frontal bone to be most affected, but in only one female with a relatively thick vault (Burial 77) was the thickness relative to the sample mean greater at the midfrontal and bregma than at vertex. However, given that the vault thickness is within the normal range (albeit at the upper extreme), there is insufficient basis for classifying this individual as anemic.

Of the individual cases described above, all include thalassemia as a differential diagnosis, despite aspects of nonconformity with standard clinical descriptions. A difficulty with using the evidence described and illustrated in clinical reports as a basis for making a diagnosis from dry bones is that clinical reports tend to describe the more extreme cases, where the evidence is radiographically visible. As a consequence of this, many textbooks describe these extreme skeletal reactions as if they should be expected in any individual suffering from a disease. An example is the already mentioned tendency to describe the "hair-on-end" appearance on radiographs of skulls as common in thalassemics. It is also clear from the clinical literature that skeletal responses to chronic anemia, and to thalassemia in particular, are many and varied, and to expect to see all, or even many, of them in a particular population is unrealistic. For example, although there were no children with the "classic" lesion of porotic hyperostosis, there are reports of clinical cases of genetic anemia in Asia where the cranium was less affected than the postcranial skeleton (Lie-Injo, 1958; Nagaratnam, 1989). The absence of cranial vault lesions does not negate the diagnosis.

In addition to the individuals described above, others, including infants, had skeletal conditions such as osteoporosis which are

TABLE 4. Proportions of the Khok Phanom Di population with medium–severe cribra orbitalia and those with additional evidence suggestive of genetic anemia

		Cribra orbitalia		Other	
	n	N	%	N	%
Adults (>14 years)	68	5	7	2	3
Children (5–14 yrs)	12	4	33	1	8
Infants (1–4 yrs)	27	6	22	5	19
Total	107	15	14	8	7

included among the characteristics described in thalassemics. However, given the multitude of bases for the development of this condition, these individuals have been excluded from the discussion. It is not prudent to assume every case of pathology in the population to be indicative of thalassemia. Conversely, that does not exclude the possibility that some or all of these infants were thalassemic and that the bony response had simply not developed to the point where distinctive changes were evident. Conclusions which can be drawn on the prevalence of anemia on the basis of the skeletal changes described must be recognized to reflect a minimum. In the Khok Phanom Di sample, ignoring the newborn infants (n = 47), the minimum proportion of individuals with evidence of anemia is listed in Table 4. Given the potential for anemia to develop from a variety of causes, only the individuals with additional skeletal evidence suggestive of genetic anemia can be included in the calculation of prevalence of the condition in the population (8/107 individuals). Using the Hardy-Weinberg formula, this would give a minimum estimate of homozygotes for thalassemia in the population of 0.065, with up to 0.44 either hetero- or homozygotes. In Thailand today, at least 40% of the population carries one of the traits (WHO, 1983). In a relatively homogeneous population such as Khok Phanom Di, the level may be higher than that at any one time. The proportion of individuals with cribra orbitalia, at 14%, is low enough that the extreme case of a genetic basis for all the anemia in the population cannot be absolutely discounted.

The genetic anemias are the result of mutations which produce either qualitative or quantitative abnormalities in the structure of the hemoglobin molecule. Qualitative abnormalities involve an alteration in the amino acid sequence of a globin chain. Although there are many of these hemoglobin variants, most are not pathological (Wickramasinghe, 1986). The best known of the hemoglobinopathies is hemoglobin (Hb) S, which results in sickle-cell anemia. Quantitative deficiences, where the rate of synthesis of one of the globin chains is depressed, result in an imbalance in the alpha and beta globin chains of the molecule, or their juvenile analogs. The amino acid sequences of the globin chains which are synthesized are usually normal. The diseases resulting from the globin chain imbalance are collectively known as the thalassemia syndromes (Weatherall and Clegg, 1981; Wickramasinghe, 1986). The modern geographic distribution of the genes underlying the hereditary anemias coincides with either the present or the past distribution of malaria, and their maintenance in populations is considered to reflect the selective advantage of heterozygotes in malarious areas, although the precise mechanism involved has not been demonstrated for all polymorphisms (Nagel and Roth, 1989; Yuthavong and Wilairat, 1993).

Modern southeast Asian populations carry genes for several of the thalassemia syndromes and hemoglobinopathies. The most prevalent are alpha-thalassemia, beta-thalassemia, HbE, and HbConstant Spring. These occur in polymorphic frequencies, with, as already noted, at least 40% of the population in Thailand carrying one of the traits. The presence of one of these genetic conditions at Khok Phanom Di is quite possible. Anemia resulting from HbS (sickle-cell anemia) is a highly unlikely explanation, because it is unknown east of India in modern populations.

Unlike hereditary anemia, there appear to be no diagnostic bone changes specific to acquired anemia. Iron-deficiency anemia results when there is an imbalance between dietary intake and loss or use. Dietary intake may be insufficient, or losses may be increased, for example, during pregnancy and lactation or through chronic gastrointestinal hemorrhage caused by hookworm infestation (Wickramasinghe, 1986). There is also a suggestion that iron deficiency can develop secondarily to iron withholding as a defense

mechanism against infection in the body (Weinberg, 1984). This is believed to be stimulated by the competition from the invading organism for serum iron, and is cited as a positive, adaptive response to infection (Stuart-Macadam, 1992), although it would be counterproductive for such an adaptation to compromise survival by causing chronic, severe anemia. Whether the people of Khok Phanom Di could have suffered from iron-deficiency anemia cannot be directly inferred from skeletal changes. Indirect evidence from the faunal and botanical remains at the site suggests that they had a diet which included adequate iron. Hookworm, another potential cause of iron-deficiency anemia, would have had a poor chance of survival on the seasonally dry soil of the site.

At Khok Phanom Di, individuals with evidence of anemia were spread through all levels of the site. If it is accepted that the anemia is genetic, this endurance of the genes implies that the population was exposed to malaria throughout the same period. Two of the four species of the malaria parasite, *Plasmodium,* which infect humans are present in southeast Asia. These are *P. falciparum,* the most severe of the four, and *P. vivax. Plasmodium* requires a suitable mosquito vector for transmission within human populations. Although most *P. falciparum* infection in modern Thailand is transmitted by mosquito vectors which favor the conditions in hilly areas rather than the coast, prior to modern large-scale control programs there were secondary vectors which are responsible for local areas of infection in lowland and coastal areas of wider southeast Asia (Anigstein, 1932; Russell et al., 1963). Two examples are *Anopheles sundaicus,* a coastal vector which breeds in brackish water, and *A. aconitus,* which breeds on exposed sheets of water such as rice fields, ponds or swamps, or in stream- or riverbeds (Bruce-Chwatt, 1980; Russell et al., 1963). The environment around Khok Phanom Di would have been ideal for the breeding of either of these species and therefore for malarial infection of the human population.

Anemia is a complication of both *P. falciparum* and *P. vivax* infections (Weatherall et al., 1983; Wickramasinghe et al., 1989). The possibility that anemia secondary to malarial infection was implicated in some of the mild cases at Khok Phanom Di cannot be absolutely excluded. Anemia in these cases can be moderate to severe, even in chronic malaria (Weatherall et al., 1983; Wickramasinghe, 1986). However, whether anemia secondary to malaria is likely to affect the skeleton is unclear. McGregor et al. (1956) recorded skeletal changes in anemic children in Africa with heavy and repeated *P. falciparum* infections, although the health of the children was compromised by other infections and nutritional factors so whether the *Plasmodium* infection was the principal cause of the anemia, and therefore of the skeletal changes, is unclear.

Cribra orbitalia may be one of the first, and often the only, lesion indicative of anemia to appear in the skeleton (Stuart-Macadam, 1989), and in adults it is likely to be the remodeled legacy of childhood anemia (Stuart-Macadam, 1985). As the anthropological "cribra orbitalia" is not recognized in clinical reports, it is possible that it occurs but remains unrecorded or unreported in anemias of various etiologies, where the skeletal response is minimal. It is possible that, in addition to the presence of genetic anemia in some of the people at Khok Phanom Di, there may have been other causes of anemia in the population.

> ". . . . (P)atients in areas where (malaria) is common often show multiple pathology, including iron or folate deficiency, bacterial or parasitic infections, genetic diseases of the red cell, and many other complicating factors" (Weatherall et al., 1983:75).

The appearance of individuals with skeletal evidence of anemia from the lowest levels of the site raises the possibility that the people of Khok Phanom Di brought the genetic means to reduce the impact of malaria with them when they migrated to the site, although whether these early burials indeed represent the first occupants of the site is not known. If they did bring the genetic anemia with them, this indicates that they or their ancestors had previously been exposed to malaria. There are several skeletal reports from other sites in Thailand which suggest a wide temporal and geographical distribution of genetic anemia, although the dating of some sites is disputed (Higham, 1989) and

in others the evidence suggested as indicative of the disease is inconclusive. The first suggestion of the presence of genetic anemia in the area during prehistory was made by Sangvichien et al. (1969), who described thick cranial vaults in adults from the prehistoric site of Ban Kao in west Thailand. This site was dated at 2500–500 BC (Sorensen and Hatting, 1967). In their report on the Ban Kao skeletal sample, Sangvichien et al. (1969:33) described the thickness of the flat bones of the skull of seven individuals as "extreme." They recorded parietal bone thicknesses of 7–11 mm, with the thickening being caused by expansion of the diploic tissue, which was described as having much coarser texture than normal. They suggested that:

> "Such thickness and coarseness of the diploic tissue occur most commonly in thalassemia diseases, although they may be observed (rarely and not to the same extent) in chronic severe iron deficiency anemia and in other congenital hemolytic anemias" (Sangvichien et al., 1969:33).

Jacob, in his study of a single skeleton from Sai Yok, also in western Thailand and dated to about 2000 BC, reported that the individual had a parietal thickness of 13 mm. Although he comments on the thickness, he described the diploe as ". . . not pathological, and intact" (1969:50). The published photograph of the section of the calvarium (Sangvichien et al., 1969:Plate XXI, 2) shows that both internal and external cortices are almost nonexistent, although the extent of any postmortem abrasion of the surfaces is not known. Several later reports on prehistoric skeletal samples from northeast Thailand have described cranial vaults in a majority of adults as thickened, and the suggestion is made that this indicates the presence of anemia, probably or possibly genetic, in the populations concerned (Pietrusewsky, 1974, 1984, 1988). There is no reason to doubt that the people of Khok Phanom Di could have been carrying the genes for one of the thalassemia syndromes when they arrived at the site.

CONCLUSION

Bony responses to a particular disease or trauma can be both highly variable and not necessarily distinctive. Given the limitations in the way in which bone as a tissue can respond, this is not surprising. The diagnosis of a disease in a population therefore depends on careful consideration of factors beyond a comparison of the skeletal evidence with published reports of clinical cases. Age at death is particularly important.

Although the suggestion of the presence of one of the hemoglobinopathies in prehistoric southeast Asian populations is not new, the skeletons of the people of Khok Phanom Di have provided the first postcranial evidence of the likely antiquity of the genes. The implication is that both the malarial parasite and the consequent human genetic response have had a long and profound influence on the lives of the people of southeast Asia.

The people of Khok Phanom Di had the energy and creativity to make full use of the wealth of natural resources available to them in maintaining crops of domesticated rice, developing a highly skilled ceramic technology, and maintaining contact with a wide trade network. Although their health appears to have been rather poor in comparison with other prehistoric populations, the richness of their culture shows that they had nevertheless successfully adapted to what may have been a potentially lethal malarial environment.

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